

AD _____

Award Number: **W81XWH-10-1-1056**

**TITLE: A Behavioral Treatment for Traumatic Brain Injury-Associated Visual Dysfunction
Based on Adult Cortical Plasticity**

PRINCIPAL INVESTIGATOR: **Dr. Uri Polat**

CONTRACTING ORGANIZATION: Tel-Aviv University
Tel Hashomer Ramat Gan 52621 Israel

REPORT DATE: December 2014

TYPE OF REPORT: Addendum to Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command Fort
Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT:

× Approved for public release; distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
1. REPORT DATE (DD-MM-YYYY) December 2014		2. REPORT TYPE Addendum to Final		3. DATES COVERED (From - To) 28 Sep 2010– 27 Sep 2014	
4. TITLE AND SUBTITLE A Behavioral Treatment for Traumatic Brain Injury-Associated Visual Dysfunction Based on Adult Cortical Plasticity				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-10-1-1056	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Dr. Uri Polat; Dr. Anna Sterkin email:urip@tau.post.ac.il				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Tel-Aviv University Department of Medicine, Physiology Goldschleger Eye Research Institute, Sheba Medical Center, Tel Hashomer Ramat Gan 52621 Israel				8. PERFORMING ORGANIZATION REPORT	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT We have a highly efficient and practical treatment technique to improve vision. We apply this proven-effective completely non-invasiveness training method with minimal equipment needs and no risks to evoke plasticity in the damaged visual cortex of patients with TBI. Despite numerous technical difficulties, we show remarkable achievements. We have first completed training of 2 control groups. After refining, the protocol was applied for training the TBI patients. The patients show robust improvements in various basic visual functions, including acuity, contrast sensitivity, and in the scotomata area tested using standard clinical visual field mapping. In one patient, the disability level, according to the National Social Security, was decreased from 60% to 30% following our treatment, indicating an enhancement in the independence of the patients in the daily life – an effect of critical social importance. These gains were accompanied by unexpected improvements in near vision, as well as in general processing speed, overall attention, cognitive processing, and involuntary eye movement suppression during fixation. These effects also supported improvement in higher level visual functions, such as reading and even driving. The patients also report substantial subjective improvement in the everyday life tasks, supported by the reports of their family members. To our best knowledge, no remedy is still available for visual deficits associated with TBI. Moreover, when presented at the World Congress On Brain Injury in March 2014, our method attracted much interest from experts in the field.					
15. SUBJECT TERMS Traumatic Brain Injury; Perceptual Learning; Behavioral Treatment; Visual Dysfunction; Cortical Plasticity					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 26	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

Table of Contents

Introduction	5
Body	6
Control Subjects	6
TBI Patients.....	14
Key Research Accomplishments	21
Reportable Outcomes.....	21
Conclusion.....	23
References	24
Appendices.....	26

Introduction

Different traumatic brain injuries are associated with visual dysfunction (Chua, Ng, Yap & Bok, 2007). Tissue damage following stroke, car accident, etc. may result in visual scotomas or other severe visual deficits. Accumulating evidence suggests that the adult visual cortex retains significant potential for experience-dependent plasticity (Fahle, 2002). A primary mechanism proposed to regulate adult plasticity is the ratio between inhibition and excitation in the cortex. Plasticity is based on neuronal excitations and is affected by pharmacological changes in the balance between neuronal excitation or inhibition (He, Hodos & Quinlan, 2006, Maya Vetencourt, Sale, Viegi, Baroncelli, De Pasquale, O'Leary, Castren & Maffei, 2008, Rozas, Frank, Heynen, Morales, Bear & Kirkwood, 2001).

A method developed in our laboratory is a psychophysical (behavioral) non-invasive paradigm that triggers plasticity by changing the balance towards excitations. Neuronal interactions in the visual processing were robustly affected by changes in the balance between excitations and inhibitions. We applied a similar paradigm earlier to treat abnormal neuronal interactions in amblyopic adults (Polat, 2008, Polat, Ma-Naim, Belkin & Sagi, 2004). We were the first to show plasticity in adults with a visual deficit that was then considered untreatable. Using a similar paradigm, we also achieved a significant improvement in individuals with presbyopia (Polat, 2009a, Polat, Schor, Tong, Zomet, Lev, Yehezkel, Sterkin & Levi, 2012b) and developmental object and face agnosia (Lev, Gilaie-Dotan, Gotthilf-Nezri, Yehezkel, Brooks, Perry, Bentin, Bonnef & Polat, 2014a). Thus, overall, our treatment induces visual enhancement of blurred or low-contrast images, an effect that is highly applicative for patients with visual dysfunction associated with TBI. Moreover, training on the same paradigm in healthy control subjects resulted in improved visual functions in young subjects with normal vision (Lev, Ludwig, Gilaie-Dotan, Voss, Sterzer, Hesselmann & Polat, 2014c, Sterkin, Yehezkel & Polat, 2012). Thus, we have a highly efficient and practical treatment technique to improve vision. We apply this proven-effective training techniques to evoke plasticity in the damaged visual cortex of patients with TBI, as our results show (see below). From the clinical perspective, the training paradigm is intended to evoke objectively evaluated improvements in various visual functions and to reduce the extent of the damaged visual fields (i.e., "restitution training").

Body

Control Subjects

We have trained one group of 21 control subjects and another (initially unplanned) group of 21 control subjects that have been trained on a modified protocol (42 control subjects in total). Following the training, there was a remarkable improvement in the objective measurements of the visual functions, including subjective improvement reported by the subjects. Importantly, there were no changes in the gaze position induced by training, indicating that the improvements in the visual functions induced by training cannot be accounted for by gaze stabilization mechanism, allowing us to conclude that the changes occurred in the brain.

All measurements of the visual functions were performed in the lab and are shown before (pretest) and after (posttest) completing 20-30 training sessions (each session on a different day). All subjects were trained in their homes.

Here we show the representative results of the healthy control subjects, categorized according to the three major visual functions.

Visual Acuity & Reading

Visual Acuity Measured With The Standard Clinical ETDRS Chart

Visual acuity measured using the ETDRS chart is a standard clinical measure of static visual acuity in the fovea, with a logarithmic relationship between the chart lines. This measurement allows us to evaluate the improvements following training in units that are relevant for clinicians.

Figure 1 shows the visual acuity measured using the standard clinical ETDRS chart (left panel) before and after training. The zero line of the ETDRS chart indicates perfect vision (i.e., 20/20) and negative values indicate supervision. There was a significant improvement of visual acuity after training, both in the left eye (Fig. 1, middle panel, 0.07 ETDRS lines, $P < 0.001$) and in the right eye (Fig. 1, right panel, 0.05 ETDRS lines, $P < 0.004$), that is by 18% and 13%, respectively. Note, that this improvement was achieved from a starting point of vision that is better the perfect vision (i.e., pretest measurements below zero in log units) towards supervision.

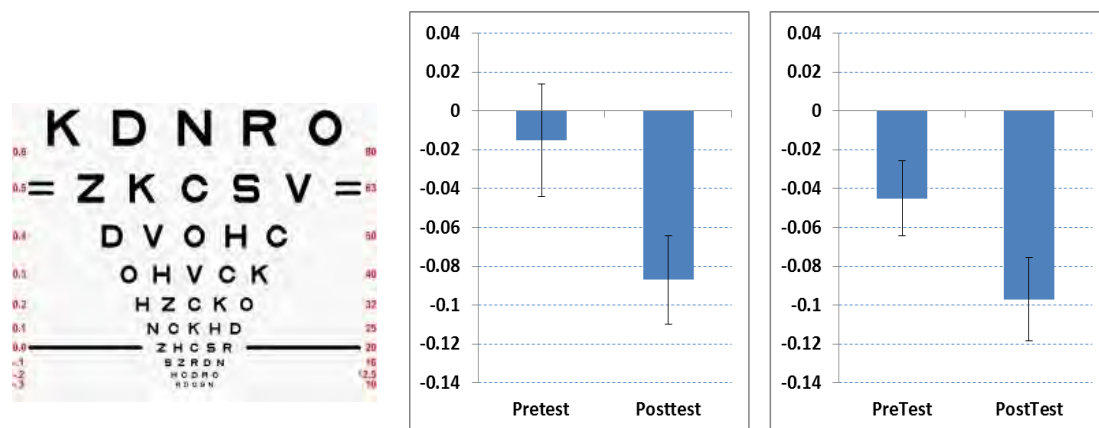


Figure 1 Training results of the healthy participants on ETDRS chart. Error bars, SEM.

Letter Crowding - A Reading Quality Measurement Using A Computerized Visual Acuity Test (E-Test)

Letter crowding during reading is the difficulty to identify letters in a line of text compared to easy identification in isolation. Crowding is widely acknowledged as a sensitive measure of visual acuity in the peripheral vision, similar to the ETDRS chart measurement of the visual activity in the fovea. Crowding increases with decreasing spacing between letters and is widely acknowledged to constitute a critical bottleneck for the higher-level processes such as consciousness, attention and recognition.

After training, crowding decreased with both the lower letter density (spacing of 4 letters) and the higher (spacing of 1 letter) (Fig. 2, all differences are significant: $P < 0.05$). Note, that the magnitude of crowding reduction in peripheral vision is similar to the improvement on the standard clinical ETDRS chart in the fovea: 0.07 log units for the spacing of 1 letter and 0.05 for the spacing of 4 letters.

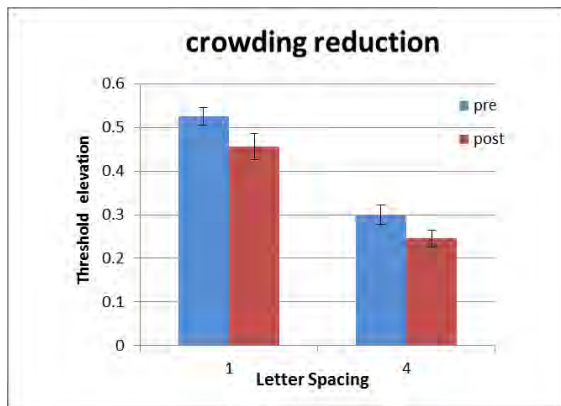


Figure 2 Training results of the healthy participants on E-test. Error bars, SEM.

Stereo Acuity

Stereo acuity measured using the digital disparity test is a measure of the ability to use the monocular disparity cues in order to perceive depth in the fovea. This measurement allows us to evaluate the unexpected improvements in visual functions following training that are relevant for clinicians.

After training, the stereo acuity was significantly improved for the two highest of the four tested disparities (Fig. 3, $P = 0.18, 0.10, 0.01$ and 0.03 for increasing disparities of 20, 40, 80 and 160 arcsec). Note, that before training the threshold of 75% correct responses was above 180 arcsec and decreased dramatically after training to about 50 arcsec.

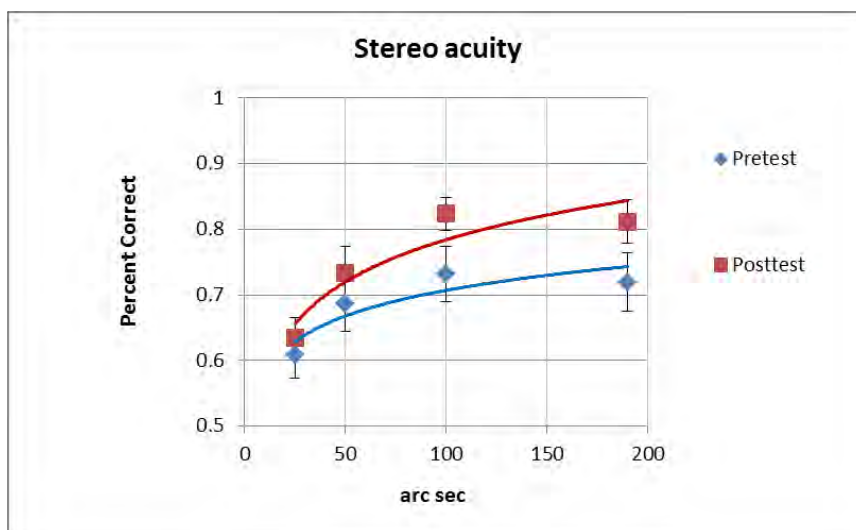


Figure 3 Training results of the healthy participants on stereo acuity for different spatial disparities. Error bars, SEM.

Contrast Sensitivity

Transient Contrast Sensitivity

Contrast sensitivity measured using the digital test with controlled short presentations, is a measure of the ability to detect minute changes in the shades of gray, both in the fovea and the periphery. Contrast sensitivity is a standard clinical measure of the basic visual function relying on neuronal processing in the primary visual cortex provides the substrate for the higher-level visual functions, such as reading. In contrast to the standard static test, the more sensitive short-presentation measurement allows us to evaluate the incremental improvements before they become measurable using the static measurements and in a more detailed manner.

After training, there was a significant improvement in contrast sensitivity measured with transient Gabor stimuli (Fig. 4). The improvement was evident both in the periphery (bottom left panel, all differences are significant in the periphery: $P < 0.002$) and in the fovea (upper left panel, significant only for the lowest contrast of the target Gabor of 5%, an expected ceiling effect for high contrast that do not leave room for improvement: $P < 0.001$). A similar pattern of results was observed for d-prime that is a standard sensitivity measure calculated from the probabilities of Hit and False-Alarm responses (right panels).

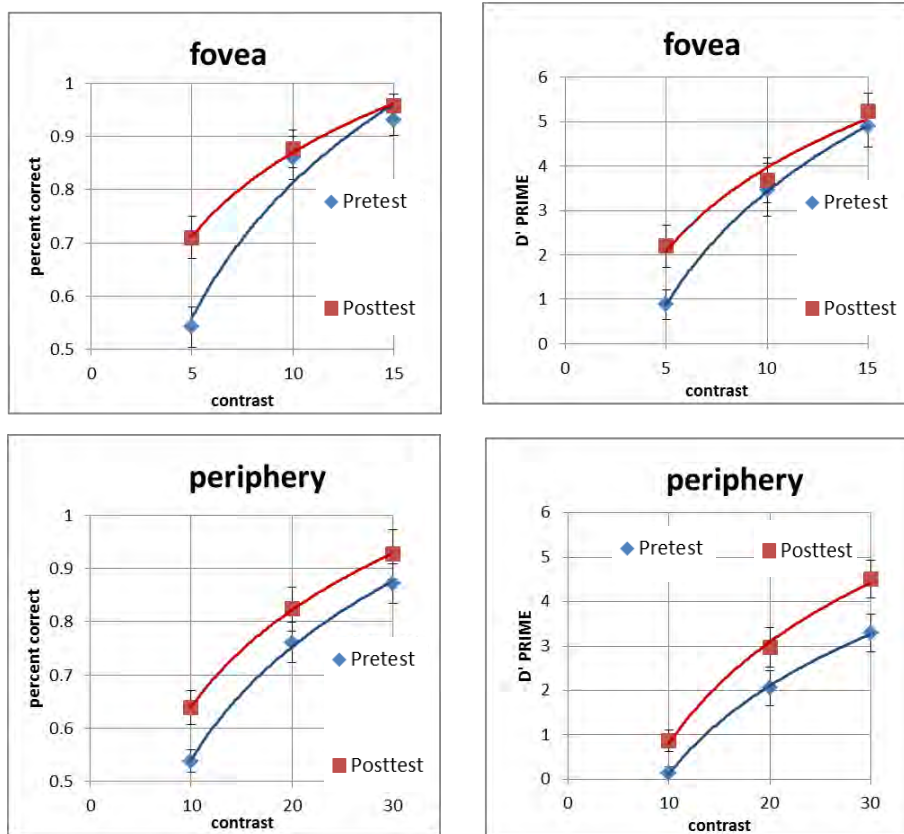


Figure 4 Training results of the healthy participants on a Transient Contrast Sensitivity task (Percent Correct and D-prime). Error bars, SEM.

Static Contrast Sensitivity Under Day Vs. Night Conditions

The static contrast sensitivity measurement allows us to evaluate the improvements in the basic visual functions following training that are relevant for clinicians. In addition, measurements were made under challenging "Night" conditions to evaluate the unexpected improvements in visual functions following training that are relevant for clinicians.

After training, there was a significant improvement in the static Contrast Sensitivity test (Fig. 5). Contrast sensitivity was measured "Day" and "Night" conditions, at three different spatial frequencies each (6, 9 and 12 cpd for "Day" and 3, 6, and 9 for "Night"). There are clear effects of the lightening conditions and of the spatial frequency on contrast detection, with significant improvement for the lowest spatial frequency of 6 cpd under "Day" conditions (upper panel, $P < 0.02$) and for the two lower spatial frequencies for the "Night" conditions (bottom panel, $P < 0.02$).

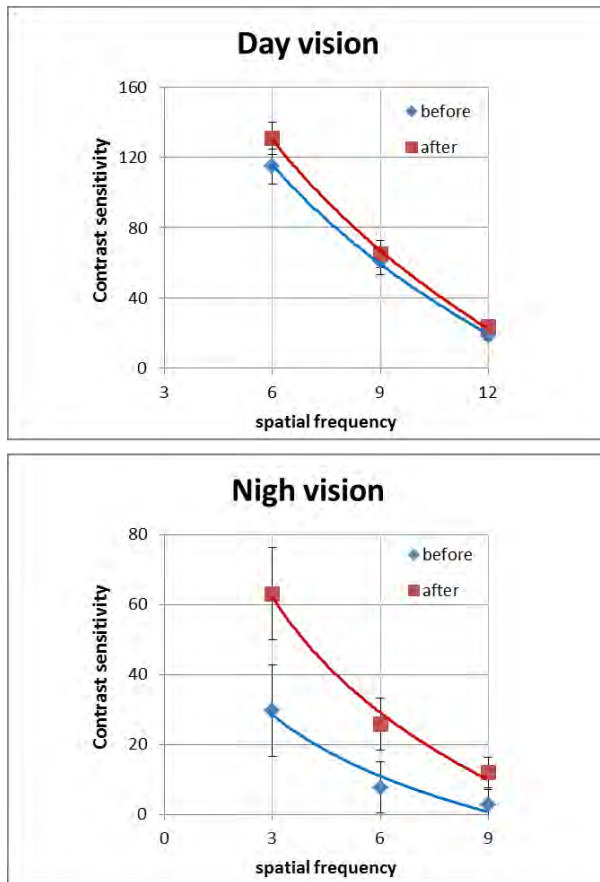


Figure 5 Training results of the healthy participants on a Static Contrast Sensitivity task under Day and Night conditions. Error bars, SEM.

Lateral Interactions In Transient Contrast Sensitivity

Lateral interaction between neurons in the primary visual cortex quantified as a modulation of the contrast sensitivity is a measure of the ability to effectively utilize neuronal networks supporting contrast detection. This ability is essential for the higher-level visual functions, such as figure-ground segregation and object detection.

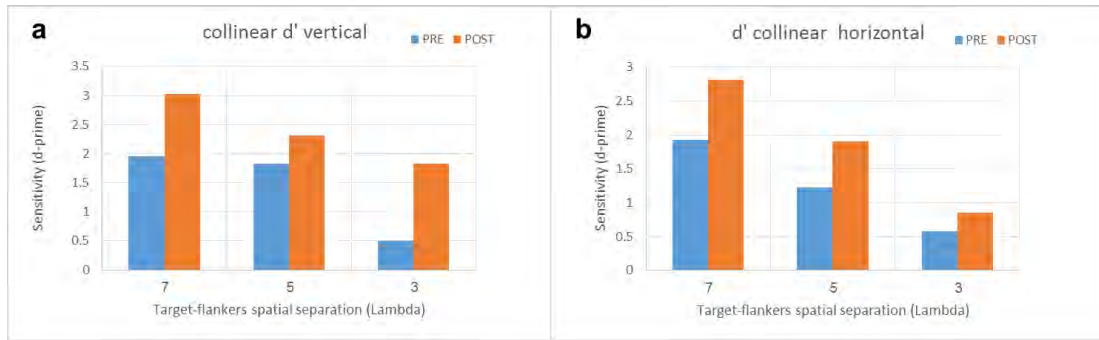


Figure 6 Lateral interactions. Contrast sensitivity facilitation measured with transient Gabor stimuli (d-prime) in healthy participants, as a function of spatial separation between the target and the flanking Gabors. The separation is measured in spatial wavelengths (Lambda). Error bars, SEM. Higher values indicate improvement.

After training, there was a significant improvement in contrast sensitivity facilitation (that is a measure of the benefit in contrast detection due to more effective inter-neuronal communication in the primary visual cortex) measured with transient Gabor stimuli with 3 different spatial separation between the low-contrast Gabor target and the flanking high-contrast collinear Gabors (Fig. 6, in periphery with the eccentricity of 4 degrees). The improvement was evident both for closer and for further spatial separations ($P < 0.04$). A similar pattern of results was observed for vertical (left panel) and horizontal (right panel) directions.

Oculomotor Parameters

These measurements allow us to evaluate to what extent changes in the gaze position induced by training in normal controls can or cannot account for improvements in the visual functions induced by training.

The data presented in Figure 7 refers to all trials (both with True and False responses), in the range [-100, 500 milliseconds] relative to stimulus onset. The left panel shows the average of the per-trial standard deviation of mean position, i.e. the "quality" parameter for each trial that is the variability of the gaze position in the given time range. The right panel shows the standard deviation of the above variability, i.e. the gaze stability across the session. As can be easily seen, there were no changes in the gaze position induced by training in normal controls, indicating that the improvements in the visual functions induced by training cannot be accounted for by gaze stabilization mechanism.

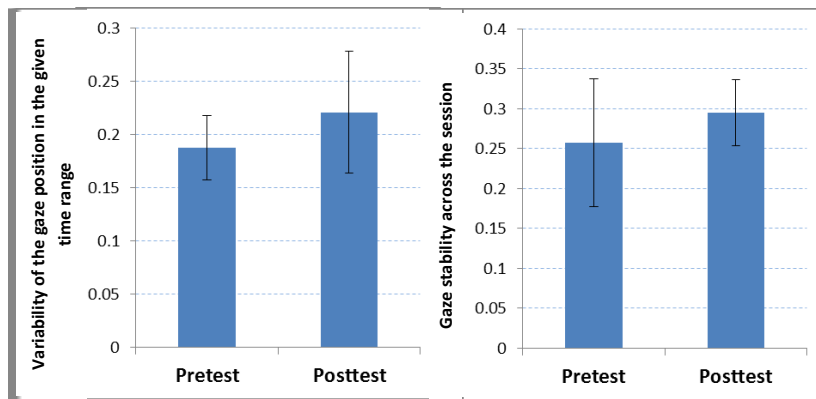


Figure 7 Training results of the healthy participants on gaze stability. Error bars, SEM.

TBI Patients

We anticipated that the pre-treatment phase of the TBI patients will require personal adjustments for each patient. Indeed, due to different type of the injury of each patient, that involve cognitive and motor limitations, we were required to personalize the psychophysical testing to the abilities of each patient. For example, such adjustments were done in the presentation time of the stimuli, adding sounds to mark the presentation time and colored symbols to ease with the detection of the temporal interval. All these adjustments required continued programming modifications and retesting. Moreover, due to physical and transportation limitations, the amount of collected data in each session is limited compared to control data. As a result, the period of the pre-treatment sessions is much longer than initially anticipated. On the other hand, this period is also necessary and can be considered as instruction period that is needed for the patients to comprehend the training procedures.

Obviously, the adjustment of the pretesting is posing the requirement to re-test control subjects on the modified parameters that the TBI patients were tested on, in order to have normative data. This led to the addition of the second group of control subjects.

Part of the training was performed at the patient's homes, in addition to their weekly regular visits to the lab. This adjustment was suggested by the Review Expert Panel and is aimed at reducing the burden from the patients to arrive few times a week to the lab. To do so, we were providing part of them with computers, providing support on internet connection and other technical issues that needed to be resolved for remote training. We have installed the training program and were receiving/sending the training sessions via the internet. In general, establishing efficient training protocol for TBI patients was a very challenging task, requiring creative solutions significantly tailored to each patient. This solution allowed acceleration of the pace of training. Moreover, the Head Trauma Rehabilitation department (Dr. Ofer Keren, Head) of the Sheba Medical Center initiated a collaboration and is interested in installing the training application on 11 iPads that are dedicated in the department for treatment.

Our latest tests indicate that three patients demonstrate unequivocal improvements in their Visual Field exams, as shown in the examples below (not all patients have visual field impairments, as this was not an inclusion criterion). Moreover, we have robustly demonstrated that these improvements cannot be accounted for by compensatory gaze-movement behaviors, thus supporting that improvements are contributed by brain plasticity following perceptual training. The observed improvement in fixation in the center of the screen that we did observe following the training in some patients allows a more reliable clinical testing of the visual field, besides its obvious positive impacts on higher visual functions relying on proper foveal fixation, such as reading.

Here we show the representative results of the TBI patients, categorized according to the three major visual functions. Most importantly, we also show examples of improved clinical visual field measurements.

Visual Acuity & Reading

Visual acuity measured with the standard clinical ETDRS Chart and a computerized visual acuity test (E-tst).

For the TBI patients, as for the control subjects, the ETDRS measurements were used as a reliable golden-standard clinical evaluation of improvements in the visual acuity. Both static and short-duration measurements allow us to gradually follow the incremental change induce by training, with subsequent training protocol adjustments.

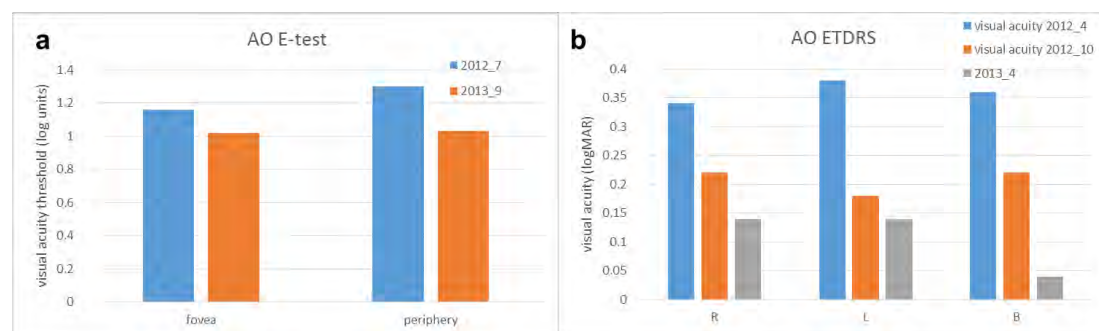


Figure 8 Visual acuity. Improvement on a) computerized visual acuity test and b) standard visual acuity chart (ETDRS) during on-going training for a representative TBI patient AO. The date of the measurements is denoted as "Year_Month". Lower values indicate improvement. Note the remarkable difference between the measurements using the electronic (a) and the static (b) measurements both due to the short vs. unlimited stimulus exposure and the intermixed central/peripheral vs. only central presentation.

Figure 8 shows visual acuity measurements using a computerized visual acuity test and the standard clinical ETDRS chart for the representative subject AO. Visual acuity in the normal controls before training is zero (20/20). There is a pronounced improvement in the visual acuity, of more than 3 ETDRS lines (above 100% improvement), towards the levels of the normal control group.

Visual acuity measured with a computerized visual acuity test & reading

For the TBI patients, as for the control subjects, the ETDRS measurements were used as a reliable golden-standard clinical evaluation of improvements in the visual acuity. Both static and short-duration measurements allow us to gradually follow the incremental change induce by training, with subsequent training protocol adjustments.

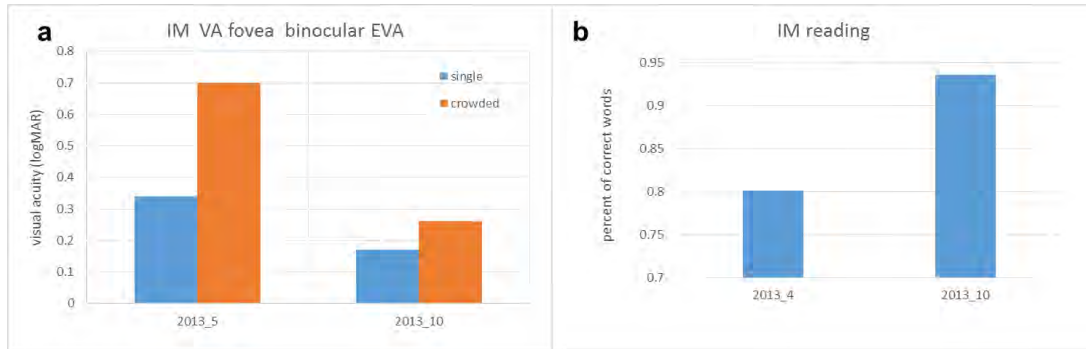


Figure 9 Visual acuity and reading. a) Improvement in visual acuity of letters measured in isolation and when surrounded by other letters for a representative TBI patient IM. Lower values indicate improvement. b) Improvement in single word covert reading for a representative TBI patient IM. The date of the measurements is denoted as "Year_Month". Higher values indicate improvement.

Figure 9 shows a profound objective improvement in both the visual acuity measurements and the reading abilities of a representative TBI patient IM following training. These findings are accompanied by a profound subjectively reported improvement (by both the patient and the family).

Contrast Sensitivity

For the TBI patients, as for the control subjects, the contrast sensitivity measurement serves as an important clinically-relevant indication of improvement, both for final evaluation and as a sensitive guide for the ongoing adjustments in the training protocol.

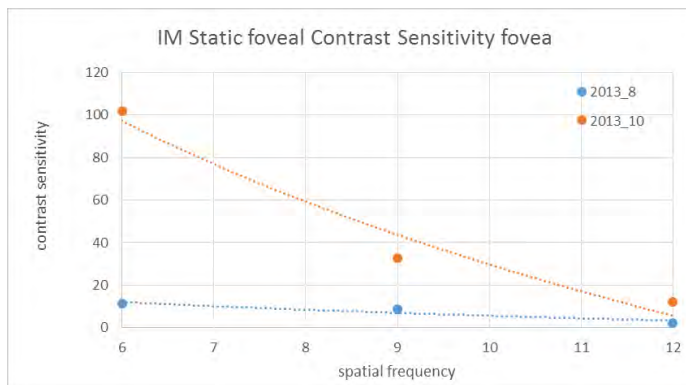


Figure 10 Contrast Sensitivity in the fovea. Improvement in contrast sensitivity measured using static foveal Gabor targets for a representative TBI patient IM. The date of the measurements is denoted as "Year_Month". Higher values indicate improvement.

Figure 10 shows contrast sensitivity improvement for static targets for the representative subject. There is a pronounced improvement for the lower spatial frequency (6 cpd, more than a 5-fold improvement), towards the levels of the normal control group. There is also a 2-fold improvement in the higher spatial frequency (9 cpd) with a trend of improvement for the highest spatial frequency (12 cpd).

Since the training methodology is based on ***lateral interactions*** between neurons, we tested the effects that flanking Gabors induced on the target Gabors for the spatial separation that induces a positive effect in normal controls ("facilitation", initially published in Polat and Sagi, 1993 and widely explored since then). The positive effect of lateral interactions reduces the detection threshold of the target Gabor, whereas a negative effect, also termed "lateral masking", induces threshold elevation for the target detection.

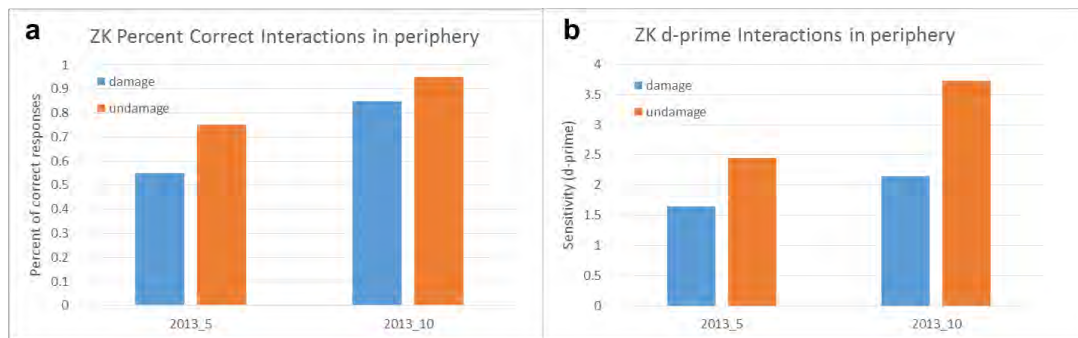


Figure 11 Improvement in contrast sensitivity due to lateral interactions measured using transient peripheral Gabor targets. Contrast sensitivity shown as a) percent of correct responses and b) sensitivity (d-prime) for a representative TBI patient ZK. The blue bars represent targets within the damaged visual field, whereas the red bars represent targets presented within the intact areas of the visual field. The date of the measurements is denoted as "Year_Month". Higher values indicate improvement.

As shown in Figure 11, there is a pronounced improvement in lateral interactions in the damaged visual field, towards the pattern that is found in the intact areas of the visual field.

Oculomotor Parameters

These measurements are critically important for the TBI patients, due to the usual suspicion regarding any sensory improvement related to a visual scotoma that it can be accounted for by a compensatory mechanism of gaze stabilization. Hence, these direct measurements allow us to evaluate to what extent changes in the gaze position (so called gaze-control) induced by training can or cannot account for improvements in the visual functions induced by training.

Figure 12 shows an example of oculomotor measurements performed during a demanding perceptual task, reflected in eye position trajectory in the horizontal direction. As can be clearly seen from Figure 12a and b, on average, in the posttest, the saccade onset time relative to the stimulus onset appears earlier. A different analysis showed that this trend is not due to any within session effect but rather a clear difference between the pre- and posttest measurements. Moreover, Figure 12c and d show that in 2-dimensions, the spread of eye position is larger in the pretest in the vertical direction compared to posttest.

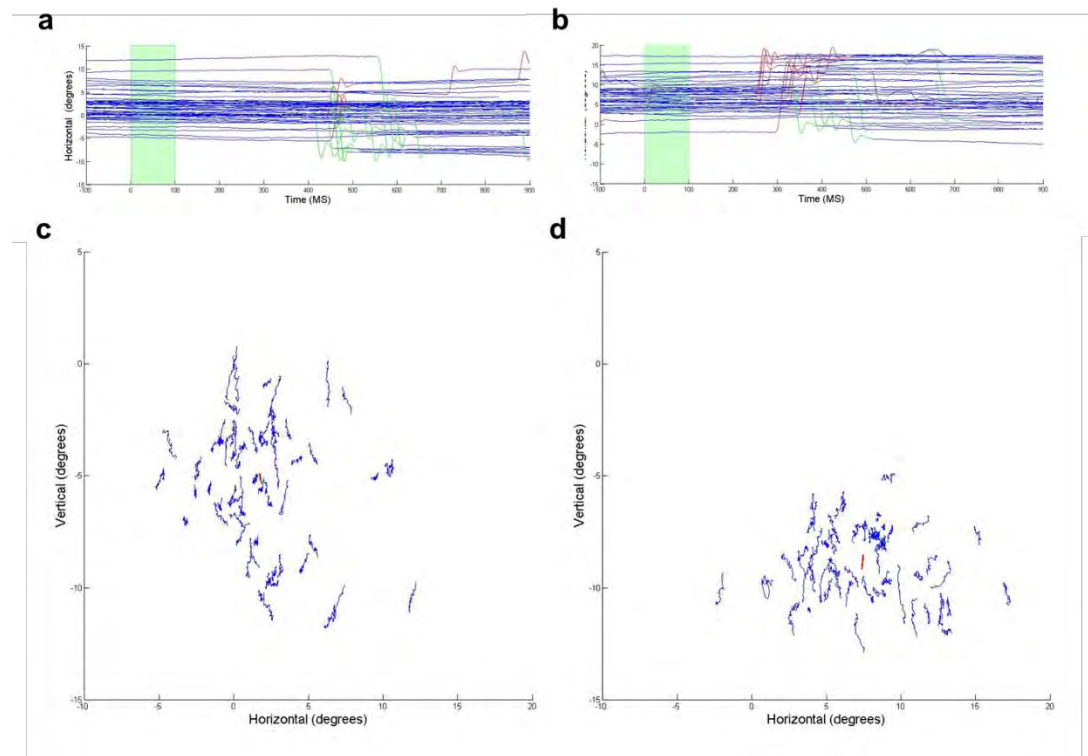


Figure 12 Eye movement trajectory. Eye position trajectory in the horizontal direction of a) pretest and b) posttest for a representative TBI patient OS. The green bars represent the stimulus presentation time, with the onset at 0. Each blue line represents the slow phase of eye movements, whereas the superimposed red and green sections are the fast saccadic movements in the left and right direction, respectively. 2-D trajectory of the same c) pre- and d) posttest measurements.

Figure 13 shows the distribution of horizontal and vertical gaze positions. The title shows that 95% percentile falls within the very narrow distribution range (below 2 degrees in each direction). The 5% of the trials could not change the results. Moreover, a displacement of 1.5-2 deg could also have no real impact (and is within the range expected for healthy population), given these are movements that are scattered around zero and not a systematic bias in any direction, thus supporting no gaze-based compensatory behavior.

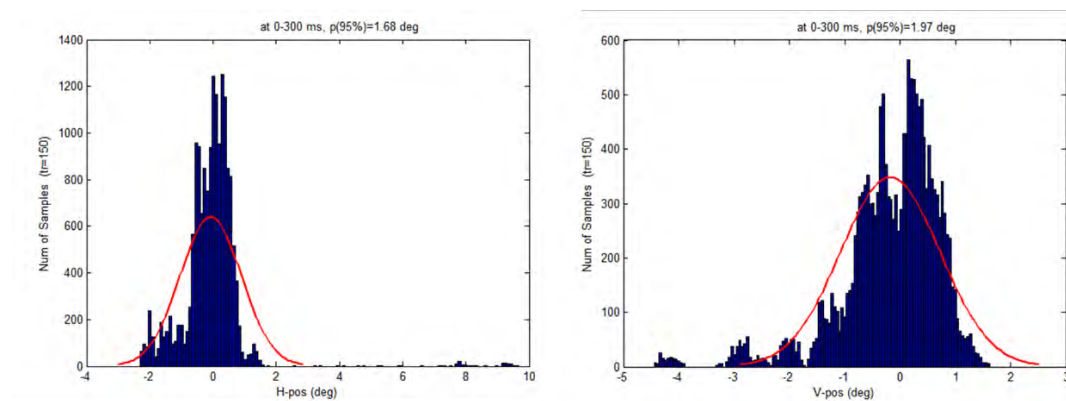


Figure 13 Trajectory of gaze the distribution of horizontal and vertical gaze positions in patient ZK. Eye tracking was performed during Gabor-target detection experiment, with randomly intermixed trials each presenting a target either in the center of the screen or in the left or the right periphery, while the subject is instructed to maintain fixation in the center of the screen throughout the whole experiment.

Visual Field

For those TBI patients that present visual scotomata using the standard clinical visual field mapping, this measurement is the most robust clinical manifestation of improvement.

Figure 14 shows a robust improvement in the scotoma area (upper right quadrant) following the training. This improvement follows robust improvements of various visual functions and constitutes the most valuable evidence of objective improvement in the visual field in clinical terms.

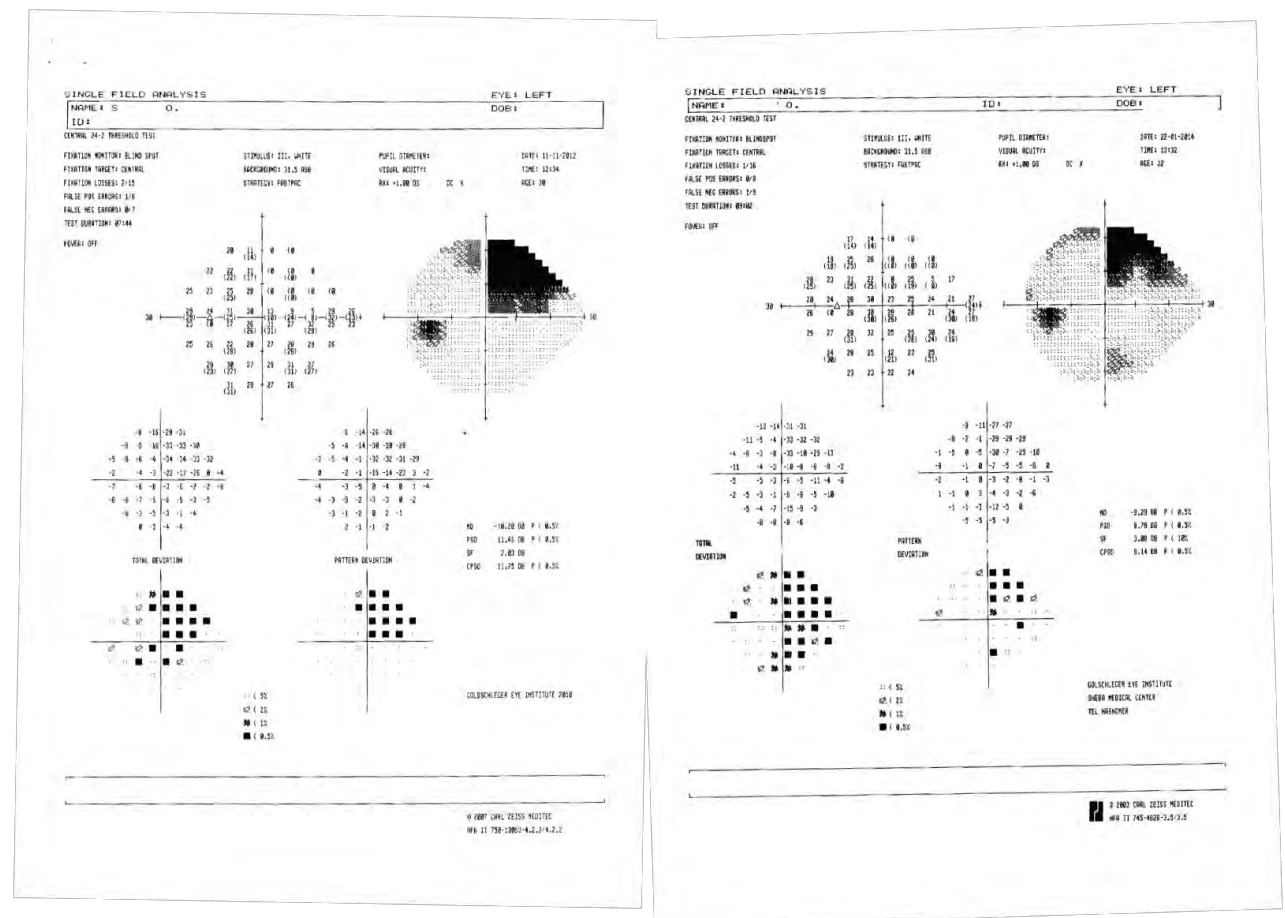


Figure 14 A robust improvement is evident in the scotoma area (upper right quadrant) in subject OS following the perceptual training, as evident from the comparison between the Visual Field exam at the beginning of the training (left) and recently (right).

In another patient, a robust improvement is also evident in the scotoma area (upper right quadrant) following the training (Fig. 15). Similarly to the above, this improvement relies on incremental improvement in the basic visual functions and is of high clinical value.

Key Research Accomplishments

- Improvements in the two control groups.
- Improvement in various visual functions that has an impact on the everyday functions.
- Validation of the training protocol suitability for patients.
- Solving technological problems to enable training of patients at their homes.
- Training of patients at their homes with measurable improvements.
- Formulation of a highly effective method for treatment of visual deficits.
- Applicability of the method to both central and peripheral visual deficits caused by TBI.
- Complete non-invasiveness of the method, with minimal equipment needs and no risks.
- Collaboration with the Head of the Trauma Rehabilitation department at Sheba Medical Center and with other medical centers, including Loewenstein Hospital Rehabilitation Center.
- Presentation of the TBI patient's data in three scientific meetings.
- Preparation of the TBI patients' data for publication.

Reportable Outcomes

- Presentation in the 3rd International Workshop on Perceptual Learning in December 2012.
- Presentation at the 10th World Congress on Brain Injury held by the International Brain Injury Association in March 2014.
- Presentation at the 34th Annual Meeting of the Israeli Society for Vision and Eye Research (ISVER) in March 2014.

- Preparation of a publication based on the data of the TBI patients.

Conclusion

We have a highly efficient and practical treatment technique to improve vision. We can apply this proven-effective training method to evoke plasticity in the damaged visual cortex of patients with TBI.

First we have completed the initial pretests, the training and the posttests in the 1st control group and the 2nd control group. After analyzing the posttest results, we have refined the protocol for training the TBI patients. Following the training, the patients show robust improvements in various basic visual functions, including acuity, contrast sensitivity, and in the scotoma area tested using standard clinical visual field mapping (Lev, Sterkin, Doron, Fried, Mandel, Bar-On & Polat, 2014d). In one patient, the disability level, according to the National Social Security, was decreased from 60% to 30% following our treatment. Such improvements enhance the independence of the patients in the daily life – an effect of critical social importance. These gains were accompanied by unexpected improvements in near vision, as well as in general processing speed, overall attention, cognitive processing (e.g., on the MoCA test and in short-term memory), and involuntary eye movement suppression during fixation. These effects also supported improvement in higher level visual functions, such as reading and even driving. The patients also report substantial subjective improvement in the everyday life tasks, supported by the reports of their family members. Since the initiation of our research on treatment of visual dysfunctions following TBI, there have not been any published breakthroughs; **therefore, no remedy is still available (Huxlin, 2008)**. Moreover, when presented at the World Congress On Brain Injury in March 2014 (Lev et al., 2014d), our method attracted much interest from experts in the field. **Therefore, we propose that our method serves an efficient and safe way to incrementally improve currently untreatable visual deficits caused by TBI:**

- We have learned a lot from this feasibility study, made many procedural changes along the Award period and are now confident we have an effective and deliverable non-invasive solution for improving visual functions beyond the expected spontaneous rehabilitation following trauma ready to be applied to a larger number of patients.
- A vast time investment was made into training for each of the TBI patients, compared to healthy control subjects and to the expected time limits for the patients. In total, 150 months were invested; this is equivalent to training 50 healthy control subjects according to the 3 months training period or 25 patients according the initially expected period of 6 months for TBI patients.
- Additional funding was obtained to continue training the patients after the Award ended – the most important of our obligations towards the patients and their families. As a result, a significant part of the patients continues the training protocol, despite the required investment in terms of time, man-power and budget.
- Our research strategy included collaboration with other medical centers, including an already issued IRB approval with Yaron Sacher, MD, Head, Dept. of TBI rehabilitation, Loewenstein Hospital Rehabilitation Center. The data of the TBI patients is currently prepared for publication.

References

- Chua, K.S., Ng, Y.S., Yap, S.G., & Bok, C.W. (2007). A brief review of traumatic brain injury rehabilitation. *Ann Acad Med Singapore*, 36 (1), 31-42.
- Fahle, M. (2002). Perceptual learning: gain without pain? *Nat Neurosci*, 5 (10), 923-924.
- He, H.Y., Hodos, W., & Quinlan, E.M. (2006). Visual deprivation reactivates rapid ocular dominance plasticity in adult visual cortex. *J Neurosci*, 26 (11), 2951-2955.
- Huxlin, K.R. (2008). Perceptual plasticity in damaged adult visual systems. *Vision Res*, 48 (20), 2154-2166.
- Lev, M., Gilaie-Dotan, S., Gotthilf-Nezri, D., Yehezkel, O., Brooks, J.L., Perry, A., Bentin, S., Bonne, Y., & Polat, U. (2014a). Training-induced recovery of low-level vision followed by mid-level perceptual improvements in developmental object and face agnosia. *Dev Sci*,
- Lev, M., Ludwig, K., Gilaie-Dotan, S., Voss, S., Sterzer, P., Hesselmann, G., & Polat, U. (2014b). Training improves visual processing speed and generalizes to untrained functions. *Sci Rep*, 4, 7251.
- Lev, M., Ludwig, K., Gilaie-Dotan, S., Voss, S., Sterzer, P., Hesselmann, G., & Polat, U. (2014c). Training improves visual processing speed. *Submitted* (
- Lev, M., Sterkin, A., Doron, R., Fried, M., Mandel, Y., Bar-On, H., & Polat, U. (2014d). Perceptual learning improves visual functions in TBI patients. *10 World congress on Brain Injury*,
- Maya Vetencourt, J.F., Sale, A., Viegi, A., Baroncelli, L., De Pasquale, R., O'Leary, O.F., Castren, E., & Maffei, L. (2008). The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science*, 320 (5874), 385-388.
- Polat, U. (2008). Restoration of underdeveloped cortical functions: evidence from treatment of adult amblyopia. *Restor Neurol Neurosci*, 26 (4-5), 413-424.

- Polat, U. (2009a). Making perceptual learning practical to improve visual functions. *Vision Res*,
- Polat, U. (2009b). Making perceptual learning practical to improve visual functions. *Vision Res*, 49 (21), 2566-2573.
- Polat, U., Ma-Naim, T., Belkin, M., & Sagi, D. (2004). Improving vision in adult amblyopia by perceptual learning. *Proc Natl Acad Sci U S A*, 101 (17), 6692-6697.
- Polat, U., & Sagi, D. (1994). Spatial interactions in human vision: from near to far via experience-dependent cascades of connections. *Proc Natl Acad Sci U S A*, 91 (4), 1206-1209.
- Polat, U., Schor, C., Tong, J., Zomet, A., Lev, M., Yehezkel, O., Sterkin, A., & Levi, D.M. (2012a). Training the brain to overcome the effect of aging on the human eye. *Scientific Reports*
- Polat, U., Schor, C., Tong, J.L., Zomet, A., Lev, M., Yehezkel, O., Sterkin, A., & Levi, D.M. (2012b). Training the brain to overcome the effect of aging on the human eye. *Sci Rep*, 2, 278.
- Rozas, C., Frank, H., Heynen, A.J., Morales, B., Bear, M.F., & Kirkwood, A. (2001). Developmental inhibitory gate controls the relay of activity to the superficial layers of the visual cortex. *J Neurosci*, 21 (17), 6791-6801.
- Sterkin, A., Yehezkel, O., Lev, M., Doron, R., Levy, Y., Levian, L., Pokroy, R., Gordon, B., Polat, U., & Ma-Naim, T. (2014). Vision improvement in pilots with presbyopia following perceptual learning. *American Academy of Ophthalmology (AAO)* (p. PO449). Chicago, US.
- Sterkin, A., Yehezkel, O., & Polat, U. (2012). Learning to be fast: gain accuracy with speed. *Vision Res*, 61, 115-124.

Appendices

10/28/13 10th World Congress on Brain Injury

MARCH 19 - 22, 2014

Perceptual learning improves visual functions in TBI patients

Abstract No. 0694

Maria Lev (1), Anna Sterkin (1), Ravid Doron (1), Moshe Fried (1), Yossi Mandel (2), Ruth Huna-Baron (3), Uri Polat (1)

(1) *Tel-Aviv University, Tel-Aviv, Israel*

(2) *Bar-Ilan University, Ramat-Gan, Israel*

(3) *Sheba Medical Center, Ramat-Gan, Israel*

Different traumatic brain injuries are associated with visual dysfunction. Accumulating evidence suggests that the adult visual cortex retains significant potential for experience dependent plasticity. A primary mechanism proposed to regulate adult plasticity is the ratio between inhibition and excitation in the cortex. We developed a psychophysical (behavioral) non-invasive paradigm that triggers plasticity by changing the balance towards excitations. Neuronal interactions in visual processing were robustly affected by changes in the balance between excitations and inhibitions. We applied our paradigm, which induces visual improvement in amblyopia [lazy eye; Polat, Ma-Naim, Belkin and Sagi, D. (2004) Improving vision in adult amblyopia by perceptual learning. *Proc Natl Acad Sci U S A*, 101(17): 6692-6697) and presbyopia [aging eye; Polat, Schor, Tong, Zomet, Lev, Yehezkel, Sterkin and Levi, (2012). Training the brain to overcome the effect of aging on the human eye. *Scientific Reports*, 2 (278)] an effect that is highly applicable for patients with visual dysfunction associated with TBI. Here we report on results obtained from TBI patients that were trained on contrast detection of Gabor targets under spatial and temporal masking conditions, targeting the improvement of collinear facilitation and temporal processing. They were trained on the fovea and periphery. The patients were trained on a PC computer from a distance of 1.5 meters, once or twice a week. Training improved lateral interactions (increased facilitation and diminished the lateral suppression when it existed) and improved visual functions such as contrast sensitivity, visual acuity, crowding, reaction time, vernier acuity, and reading. There was also improvement in the pattern of eye movements and fixation. Although the previously reliable visual field was not measurable, after training, the pattern of fixation enabled measurement of a reliable visual field. Thus, the visual improvements are not due to development of eye movement or a fixation strategy to overcome the visual deficiencies, rather they are due to real improvement of the neural network involved in visual processing in the brain.

**34th Annual Meeting of the Israeli Society for Vision & Eye Research (ARVO
Chapter Affiliate)
Avenue Congress Center, Airport City
26th-27th March, 2014**

Improving visual functions in TBI patients by perceptual learning

Sterkin Anna (1,2), Lev Maria (1), Doron Ravid (1), Fried Moshe (1),
Mandel Yossi (3) Dobin Genady (1), Ruth Huna-Baron(1,4) , Polat Uri
(1,2)

(1) Faculty of Medicine, Goldschleger Eye Research Institute, Sheba Medical Center, Tel Aviv University, Israel, (2) GlassesOff Inc., USA, (3) The Mina&Everard Goodman Faculty of Life Sciences, Bar Ilan University, Ramat Gan, Israel, (4) Neuro-Ophthalmology Unit Goldschleger Eye Institute, Sheba Medical Center, Israel

Purpose: Accumulating evidence suggests that the adult visual cortex retains significant potential for experience-dependent plasticity. A primary mechanism proposed to regulate adult plasticity is the ratio between inhibition and excitation in the cortex. It is widely acknowledged that neuronal interactions in visual processing are robustly affected by changes in the balance between excitations and inhibitions.

We had previously developed a psychophysical (behavioral) non-invasive paradigm that triggers plasticity by changing the balance towards excitations under the conditions of spatial and temporal masking. In our earlier studies, our paradigm induced significant improvements in amblyopia (Polat, Ma-Naim, Belkin and Sagi

(2004) Improving vision in adult amblyopia by perceptual learning. Proc Natl Acad Sci U S A 101(17): 6692-6697) and presbyopia (Polat, Schor, Tong, Zomet, Lev, Yehezkel, Sterkin and Levi (2012). Training the brain to overcome the effect of aging on the human eye. Scientific Reports, 2: 278). Severe traumatic brain injuries (TBI) are sometimes associated with visual dysfunction which has no effective treatment. Here we applied perceptual training paradigm to patients suffering from visual dysfunction following TBI.

Methods: Patients were trained on contrast detection of foveal and peripheral Gabor targets under spatial and temporal masking conditions, targeting the improvement of both collinear facilitation and temporal processing. Patients were trained on a PC computer from a distance of 1.5 meters, once or twice a week.

Results: Training improved lateral interactions, measured as an increase in facilitation and a decrease in suppression, if existed. These gains were generalized into improvements in the basic visual functions, such as contrast sensitivity, visual acuity, crowding, reaction time, and Vernier acuity, as well as in higher visual functions, such as reading. There was also improvement in the oculomotor parameters, both in the pattern of eye movements and during fixation. Moreover, in several patients, training caused improvements in eye fixation, thus significantly increasing the reliability of visual field testing.

Conclusions: The results allow us to conclude that the visual improvements are not due to the development of a compensational eye movement or fixation strategy to overcome the visual deficiencies, but rather due to improvements of the neural networks involved in the basic visual processing in the brain.